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(54) Title: SPIRO PIPERIDINES AND HOMOLOGS WHICH PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

There are disclosed certain novel compounds identified as spiro piperidines and homologs which promote the release of growth hormone in humans and animals. This property can be utilized to promote the growth of food animals to render the production of edible meat products more efficient, and in humans, to treat physiological or medical conditions characterized by a deficiency in growth hormone secretion, such as short stature in growth hormone deficient children, and to treat medical conditions which are improved by the anabolic effects of growth hormone. Growth hormone releasing compositions containing such spiro compounds as the active ingredient thereof are also disclosed.

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TITLE OF THE INVENTION
SPIRO PIPERIDINES AND HOMOLOGS WHICH PROMOTE RELEASE OF GROWTH HORMONE

BACKGROUND OF THE INVENTION

Growth hormone, which is secreted from the pituitary, stimulates growth of all tissues of the body that are capable of growing. In addition, growth hormone is known to have the following basic effects on the metabolic processes of the body:

1. Increased rate of protein synthesis in all cells of the body;
2. Decreased rate of carbohydrate utilization in cells of the body;
3. Increased mobilization of free fatty acids and use of fatty acids for energy.

A deficiency in growth hormone secretion can result in various medical disorders, such as dwarfism.

Various ways are known to release growth hormone. For example, chemicals such as arginine, L-3,4-dihydroxyphenylalanine (L-DOPA), glucagon, vasopressin, and insulin induced hypoglycemia, as well as activities such as sleep and exercise, indirectly cause growth hormone to be released from the pituitary by acting in some fashion on the hypothalamus perhaps either to decrease somatostatin secretion or to increase the secretion of the known secretagogue growth hormone releasing factor (GRF) or an unknown endogenous growth hormone-releasing hormone or all of these.

In cases where increased levels of growth hormone were desired, the problem was generally solved by providing exogenous growth hormone or by administering GRF or a peptidal compound which stimulated growth hormone production and/or release. In either case the peptidyl nature of the compound necessitated that it be

administered by injection. Initially the source of growth hormone was the extraction of the pituitary glands of cadavers. This resulted in a very expensive product and carried with it the risk that a disease associated with the source of the pituitary gland could be transmitted to the recipient of the growth hormone. Recently, recombinant growth hormone has become available which, while no longer carrying any risk of disease transmission, is still a very expensive product which must be given by injection or by a nasal spray.

Other compounds have been developed which stimulate the release of endogenous growth hormone such as analogous peptidyl compounds related to GRF or the peptides of U.S. Patent 4,411,890. These peptides, while considerably smaller than growth hormones are still susceptible to various proteases. As with most peptides, their potential for oral bioavailability is low. The instant compounds are non-peptide analogs for promoting the release of growth hormone which are stable in a variety of physiological environments and which may be administered parenterally, nasally or by the oral route.

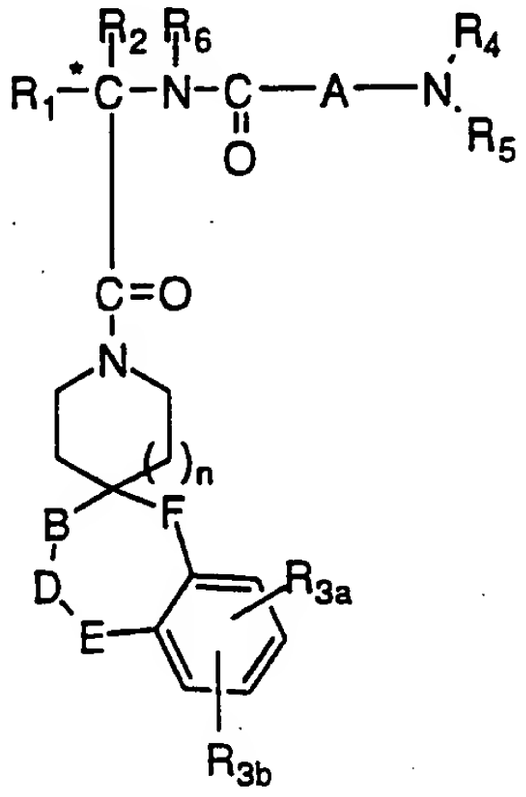
SUMMARY OF THE INVENTION

The instant invention covers certain spiro compounds which have the ability to stimulate the release of natural or endogenous growth hormone. The compounds thus have the ability to be used to treat conditions which require the stimulation of growth hormone production or secretion such as in humans with a deficiency of natural growth hormone or in animals used for food production where the stimulation of growth hormone will result in a larger, more productive animal. Thus, it is an object of the instant invention to describe the spiro compounds. It is a further object of this invention to describe procedures for the preparation of such compounds. A still further object is to describe the use of such compounds to increase the secretion of growth hormone in humans and animals. A still further object of this invention is to describe compositions containing the spiro compounds for the use of treating humans and animals so as to increase

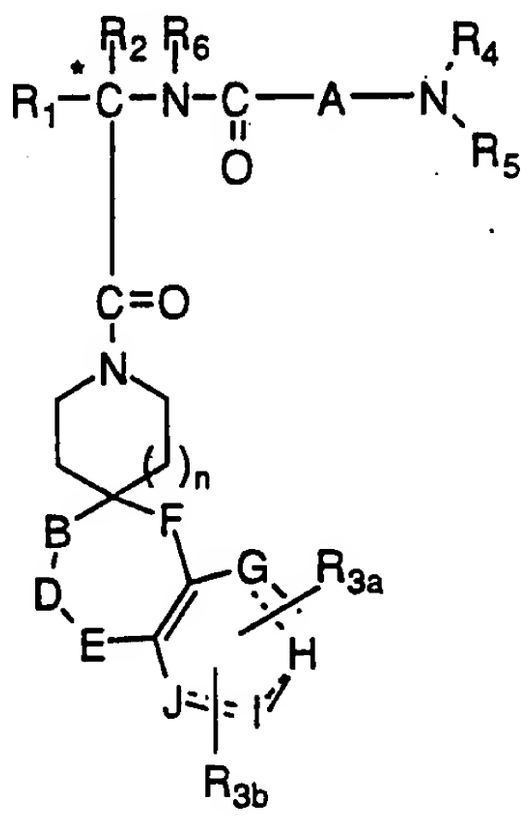
the level of growth hormone secretions. Further objects will become apparent from a reading of the following description.

DESCRIPTION OF THE INVENTION

The novel spiro compounds of the instant invention are best described in the following structural formulas I and II:



Formula I



Formula II

R_1 is C_1-C_{10} alkyl, aryl, aryl (C_1-C_6 alkyl) and C_3-C_7 cycloalkyl (C_1-C_6alkyl) or C_1-C_5alkyl-K-C_1-C_5 alkyl, aryl(C_0-C_5alkyl)-K-(C_1-C_5 alkyl), C_3-C_7 cycloalkyl(C_0-C_5 alkyl)-K-(C_1-C_5 alkyl) where K is O, S(O)m, N(R_2)C(O), C(O)N(R_2), OC(O), C(O)O, or -CR_2=CR_2- or -C≡C- where the aryl groups are defined below and the R_2 and alkyl groups may be futher substituted by 1 to 9 halogen, S(O)mR_{2a}, 1 to 3 OR_{2a} or C(O)OR_{2a} and the aryl groups may be further substituted by phenyl, phenoxy, halophenyl, 1-3 C_1-C_6 alkyl, 1 to 3 halogen, 1 to 2 OR_2, methylenedioxy, S(O)mR_2, 1 to 2 CF_3, OCF_3, nitro, N(R_2)(R_2), N(R_2)C(O)R_2, C(O)OR_2, C(O)N(R_2)(R_2), SO_2N(R_2)(R_2), N(R_2)S(O)2 aryl or N(R_2)SO_2R_2;

R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_7 cycloalkyl, and where two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_3-C_8 cyclic ring optionally including oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_6 alkyl, OR_2, cyano, OCF_3, methylenedioxy, nitro, $S(O)_mR$, CF_3 or $C(O)OR_2$ and when R_{3a} and R_{3b} are in an ortho arrangement, they may be joined to form a C_5 to C_8 aliphatic or aromatic ring optionally including 1 or 2 heteroatoms selected from oxygen, sulfur or nitrogen;

R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 3 hydroxy, 1 to 3 C_1-C_{10} alkanoyloxy, 1 to 3 C_1-C_6 alkoxy, phenyl, phenoxy, 2-furyl, C_1-C_6 alkoxycarbonyl, $S(O)_m(C_1$-C_6 alkyl); or R_4 and R_5 can be taken together to form $-(CH_2)_rL_a(CH_2)_s-$ where L_a is $C(R_2)_2$, O, $S(O)_m$ or $N(R_2)$, r and s are independently 1 to 3 and R_2 is as defined above;

R_6 is hydrogen or C_1-C_6 alkyl;

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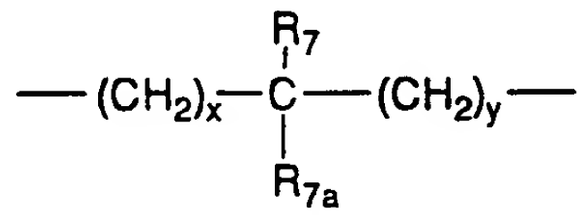
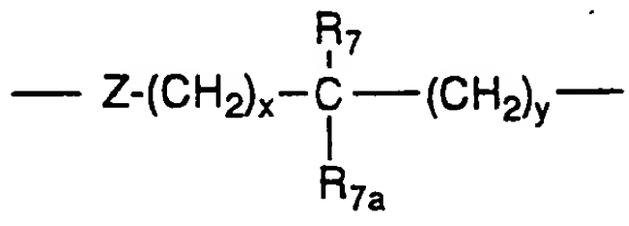


or



where x and y are independently 0-3;
Z is N-R_2 or O;
R_7 and R_{7a} are independently hydrogen, C_1-C_6 alkyl, OR_2, trifluoromethyl, phenyl, substituted C_1-C_6 alkyl where the substituents are imidazolyl, phenyl, indolyl, p-hydroxyphenyl, OR_2, 1 to 3 fluoro, $S(O)_mR_2$, $C(O)OR_2$, C_3-C_7 cycloalkyl, $N(R_2)(R_2)$, $C(O)N(R_2)(R_2)$; or R_7 and R_{7a} can independently be joined to one or both of R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 5 carbons atoms;

B, D, E, and F are independently $C(R_8)(R_{10})$, O, C=0, $S(O)_m$, or NR_9, such that one or two of B,D,E, or F may be optionally missing to provide a 5, 6, or 7 membered ring; and provided that B, D, E and F can be $C(R_8)(R_{10})$ or C=O only when one of the remaining B, D, E and F groups is simultaneously O, S(O)m or NR_9; B and D or D and E taken together may be $N=CR_{10}$- or $CR_{10}=N$ or B and D or D and E taken together may be $CR_8=CR_{10}$ provided one of the other of B and E or F is simultaneously O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, $(CH_2)_q$ $C(O)OR_2$, $(CH_2)_q$ $C(O)O(CH_2)_q$ aryl or $(CH_2)_q$ (1H-tetrazol-5-yl) and the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_8 alkyl, 1 to 3 OR_2 or 1 to 2 $C(O)OR_2$;

R_9 is R_2, $(CH_2)_q$ aryl, $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO_2(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl, $C(O)OR_2$, 1-H-tetrazol-5-yl, SO_3H, $SO_2NHC{\equiv}N$, $SO_2N(R_2)$aryl, $SO_2N(R_2)(R_2)$ and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_4 alkyl, and the R_2 and aryl may be optionally further substituted by 1 to 3 OR_{2a}, $O(CH_2)_q$ aryl, 1 to 2 $C(O)OR_{2a}$, 1 to 2 $C(O)O(CH_2)_q$ aryl, 1 to 2 $C(O)N(R_{2a})(R_{2a})$, 1 to 2 $C(O)N(R_{2a})(CH_2)_q$ aryl, 1 to 5 halogen, 1 to 3 C_1-C_4 alkyl, 1,2,4-triazolyl, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, $S(O)_mR_{2a}$, $C(O)NHSO_2(CH_2)q$ aryl, $SO_2NHC{\equiv}N$, $SO_2NHC(O)R_{2a}$.

$SO_2NHC(O)(CH_2)_q$aryl, $N(R_2)C(O)N(R_{2a})(R_{2a})$, $N(R_{2a})C(O)N(R_{2a})(CH_2)_q$ aryl, $N(R_{2a})(R_{2a})$, $N(R_{2a})C(O)R_{2a}$, $N(R_{2a})C(O)(CH_2)_q$ aryl, $OC(O)N(R_{2a})(R_{2a})$, $OC(O)N(R_{2a})(CH_2)_q$ aryl; $SO_2(CH_2)_qCONH$-$(CH_2)_wNHC(O)R_{11}$, where w is 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0, 1 or 2;

n is 1 or 2;

q can optionally be 0, 1, 2, 3, or 4; and

G, H, I and J are carbon, nitrogen, sulfur or oxygen atoms, such that atleast one is a heteroatom and one of G, H, I or J may be optionally missing to afford 5 or 6 membered heterocyclic aromatic rings; and pharmaceutically acceptable salts and individual diastereomers thereof.

In the above structural formulas and throughout the instant specification, the following terms have the indicated meanings:

The alkyl groups specified above are intended to include those alkyl groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkyl groups are methyl, ethyl, propyl, ethinyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, isohexyl, allyl, propenyl, butenyl, butadienyl and the like.

The alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a straight or branched configuration which may optionally contain double or triple bonds. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propinyloxy, isobutenyloxy, 2-hexenyloxy, and the like.

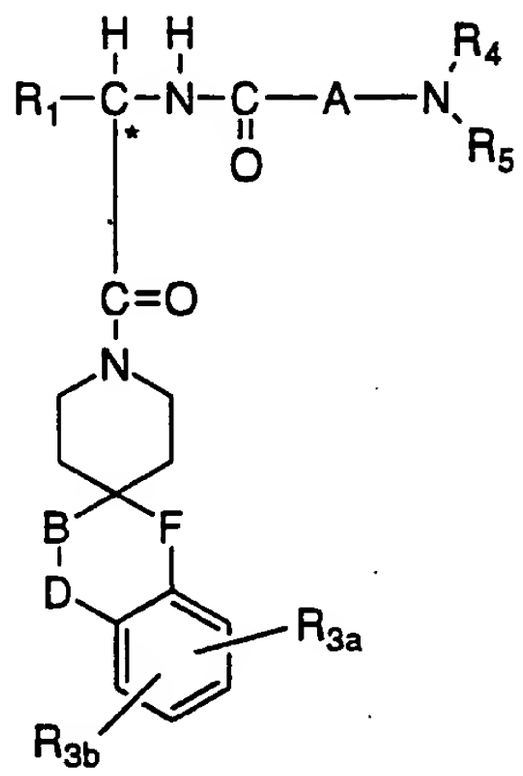
The term "halogen" is intended to include the halogen atom fluorine, chlorine, bromine and iodine.

The term "aryl" is intended to include phenyl and naphthyl and aromatic residues of 5- and 6- membered rings with 1 to 3

heteroatoms or fused 5 or 6 membered bicyclic rings with 1 to 3 heteroatoms of nitrogen, sulfur or oxygen. Examples of such heterocyclic aromatic rings are pyridine, thiophene, benzothiophene, tetrazole, indole, N-methylindole, dihydroindole, indazole, N-formylindole, benzimidazole, thiazole, furan, pyrimidine, and thiadiazole.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other.

Preferred compounds of the instant invention are:



Formula III

where R_1 is C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl), C_3-C_6 cycloalkyl (C_1-C_4 alkyl), (C_1-C_4 alkyl)-K-(C_1-C_4 alkyl), aryl(C_0-C_5alkyl)-K-(C_1-C_4 alkyl), (C_3-C_7cycloalkyl)(C_0-C_5 alkyl)-K-(C_1-C_4alkyl) where K is O, $S(O)_m$, $-CR_2=CR_2-$, $-C\equiv C-$, or $N(R_2)C(O)$ where R_2 and the alkyl groups may be further substituted by 1 to 7 halogen, $S(O)_mC_1$-C_4 alkyl, OR_{2a} or $C(O)OR_{2a}$ and the aryl groups may be further substituted by 1-2 C_1-C_4 alkyl, 1 to 2 halogen, 1 to 2 OR_2,

CF_3, OCF_3, methylenedioxy, $S(O)_mR_2$, $SO_2N(R_2)(R_2)$, $N(R_2)SO_2R_2$ or $C(O)OR_2$;

R_2 is hydrogen, C_1-C_6 alkyl, C_3-C_7cycloalkyl, and, if two C_1-C_6 alkyl groups are present on one atom, they may be optionally joined to form a C_4-C_6 cyclic ring optionally including 1 to 2 heteroatoms selected from oxygen, sulfur or NR_{2a};

R_{2a} is hydrogen or C_1-C_6 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_4 alkyl, OR_2, methylenedioxy, nitro, $S(O)_mC_1$-C_4alkyl, CF_3 or $C(O)OR_2$;

R_4 and R_5 are independently hydrogen, C_1-C_6 alkyl, substituted C_1-C_6 alkyl where the substituents may be 1 to 5 halo, 1 to 2 hydroxy, 1 to 2 C_1-C_6 alkanoyloxy, 1 to 2 C_1-C_6 alkyloxy or $S(O)_m(C_1$-C_4 alkyl);

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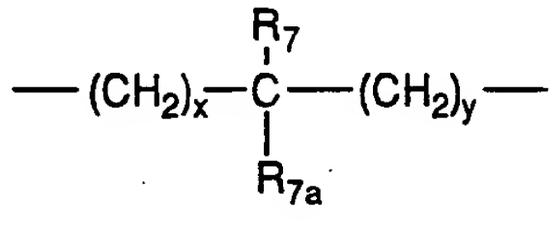

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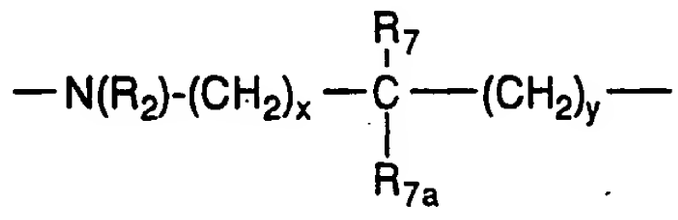


where x and y, are independently 0, 1, or 2;
R_7 and R_{7a} are independently hydrogen, C_1-C_4 alkyl, substituted

C_1-C_4 alkyl where the substituents are from 1 to 3 fluoro or imidazolyl, phenyl, indolyl, $S(O)_mC_1$-C_4alkyl, $C(O)OR_2$ or R_7 and R_{7a} can independently be joined to one or both of the R_4 and R_5 groups to form alkylene bridges between the teminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups, wherein the bridge contains 1 to 3 carbon atoms;

B, D and F are independently $C(R_8)(R_{10})$, O, C=O, $S(O)_m$ or NR_9 such that one of B, D or F may be optionally missing to provide a 5 or 6 membered ring and provided that one of B, D and F is $C(R_8)(R_{10})$ or C=O only when one of the remaining B, D and F groups is simultaneously O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2, OR_2, $(CH_2)_q$ aryl, $(CH_2)_qC(O)OR_2$, $(CH_2)_qC(O)O(CH_2)_q$ aryl, $(CH_2)_q$(1H-tetrazol-5-yl) and the aryl may be optionally substituted by 1 to 3 halo, 1 to 2 C_1-C_4 alkyl, 1 to 3 OR_2 or 1 to 2 $C(O)OR_2$;

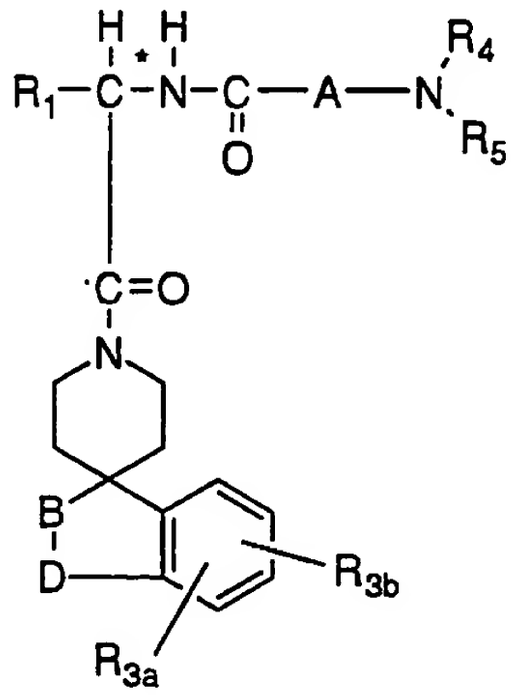
R_9 is R_2, $(CH_2)_q$ aryl, $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO_2(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl, 1-H-tetrazolyl-5-yl, $SO_2NHC{\equiv}N$, SO_2NR_2 aryl, $SO_2N(R_2)(R_2)$ and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_2 alkyl and the R_2 may be optionally substituted by 1 to 2 OR_{2a}, $O(CH_2)_q$ aryl, 1 to 2 $C(O)OR_{2a}$, $C(O)N(R_{2a})(R_{2a})$, $S(O)_mR_{2a}$, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, $C(O)NHSO_2(CH_2)_q$ aryl, $N(R_{2a})C(O)N(R_{2a})(R_{2a})$ or $N(R_{2a})C(O)N(R_{2a})(CH_2)_q$ aryl and the aryl may be optionally substituted by 1 to 2 OR_{2a}, 1 to 2 halogen, 1 to 2 C_1-C_4 alkyl, $C(O)OR_{2a}$ or 1-H-tetrazol-5-yl; $SO_2(CH_2)_w$ $CONH(CH_2)_w$ $NHC(O)R_{11}$, where w = 2-6 and R_{11} may be biotin, aryl, or aryl substituted by 1 or 2 OR_2, 1-2 halogen, azido or nitro;

m is 0,1, or 2;
q can optionally be 0, 1, 2 or 3; and

the aryl group is phenyl, napthyl, pyridyl, thienyl, indolyl, thiazolyl or pyrimidinyl,
and the pharmaceutically acceptable salts and individual diastereomers thereof.

Still further preferred compounds are realized when F is not present in Compound III.

Thus, further preferred compounds of the instant invention are realized in structural formula IV.



IV

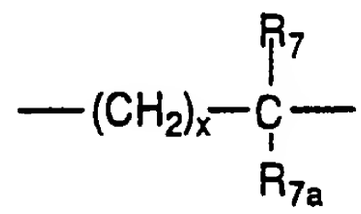
R_1 is C_1-C_{10} alkyl, aryl (C_1-C_4 alkyl), C_5-C_6cycloalkyl (C_1-C_4 alkyl) or (C_1-C_4 alkyl)-K-C_1-C_2alkyl-, aryl(C_0-C_2alkyl)-K-(C_1-C_2 alkyl), C_3-C_6cycloalkyl (C_0-C_2alkyl)-K-(C_1-C_2alkyl), where K is O or $S(O)_m$, and the aryl groups may be further substituted by 1 to 2 C_1-C_4 alkyl, 1 to 2 halogen, OR_2, $C(O)OR_2$, CF_3 or $S(O)_mR_2$;

R_2 is hydrogen, C_1-C_4 alkyl, cyclo C_3-C_6alkyl, and, if two C_1-C_4 alkyls are present on one atom, they may be optionally joined to form a C_5-C_6 cyclic ring optionally including the heteroatoms oxygen or NR_{2a}:

R_{2a} is hydrogen or C_1-C_4 alkyl;

R_{3a} and R_{3b} are independently hydrogen, halogen, C_1-C_4 alkyl, $C(O)OR_2$, hydroxy, C_1-C_4 alkoxy, $S(O)_mC_1$-C_4 alkyl or CF_3;

R_4 and R_5 are independently hydrogen, C_1-C_4 alkyl, substituted C_1-C_4 alkyl where the substituents may be 1 to 2 hydroxy or $S(O)_m$ (C_1-C_3alkyl);

A is: 

where x is 0 or 1;

R_7 and R_{7a} are independently hydrogen, C_1-C_3 alkyl; or R_7 and R_{7a} can independently be joined to one or both of the R_4 and R_5 groups to form alkylene bridges between the terminal nitrogen and the alkyl portion of the R_7 or R_{7a} groups to form 5 or 6 membered rings containing the terminal nitrogen;

B and D are independently $C(R_8)(R_{10})$, C=O, O, $S(O)_m$, NR_9 provided that one of B and D can be $C(R_8)(R_{10})$ or C=O only when the other of B and D is O, $S(O)_m$ or NR_9;

R_8 and R_{10} are independently hydrogen, R_2 or $(CH_2)_q$ aryl, and the aryl may be optionally substituted by 1 to 2 of halo, 1 to 2 C_1-C_4 alkyl, OR_2 or 1 to 2 $C(O)OR_2$;

R_9 is $C(O)R_2$, $C(O)(CH_2)_q$ aryl, SO_2R_2, $SO(CH_2)_q$ aryl, $C(O)N(R_2)(R_2)$, $C(O)N(R_2)(CH_2)_q$ aryl and the $(CH_2)_q$ may be optionally substituted by 1 to 2 C_1-C_2 alkyl and the R_2 may be optionally substituted by 1 to 2 of OR_{2a}, $O(CH_2)_q$ aryl, $C(O)OR_{2a}$,

$C(O)N(R_{2a}(R_{2a})$, $S(O)mR_{2a}$, 1-H-tetrazol-5-yl, $C(O)NHSO_2R_{2a}$, or $N(R_{2a})C(O)N(R_{2a})(R_{2a})$ and the aryl may optionally be substituted by 1 to 2 OR_{2a}, 1 to 2 halogen, 1 to 2 C_1-C_2 alkyl, $C(O)OR_{2a}$, 1-H-tetrazol-5-yl or $S(O)_mR_{2a}$;

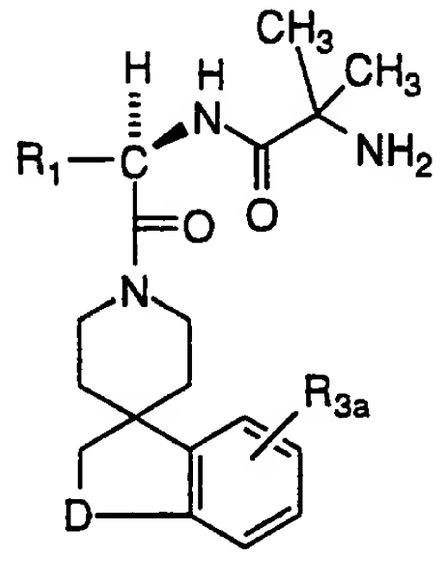
$SO_2(CH_2)_qCONH(CH_2)_wNHC(O)R_{11}$ where w = 2-6 and R_{11} may optionally be biotin, aryl, and an aryl be optionally substituted by 1 to 2 OR_2, 1-2 halogen, azido, nitro;

m is 0, 1 or 2;

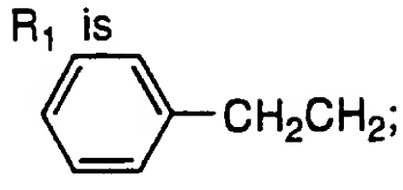
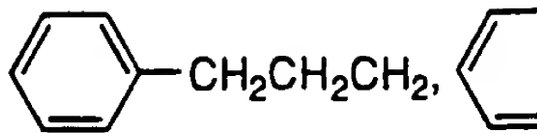
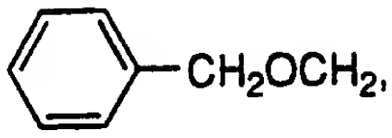
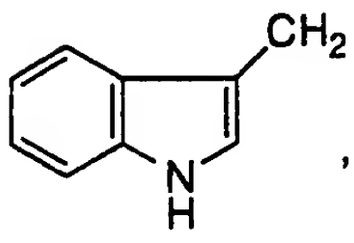
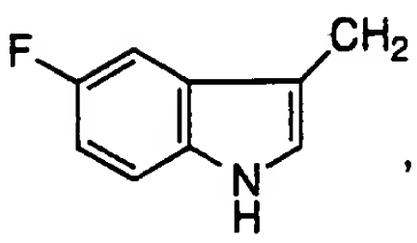
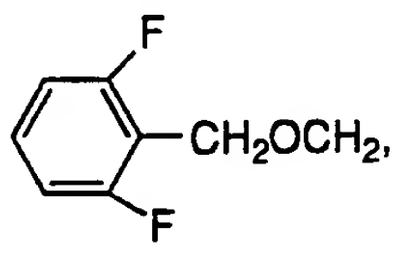
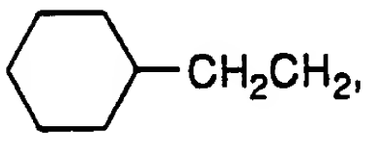
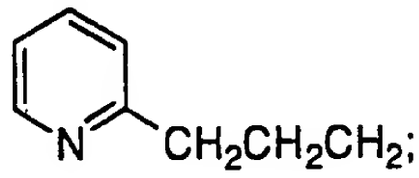
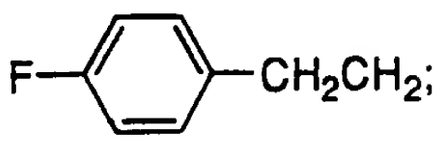
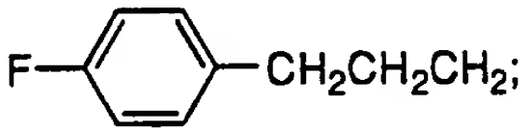
q can optionally be 0, 1, 2 or 3;

aryl is phenyl, napthyl, pyridyl, indolyl, thienyl or tetrazolyl and the pharmaceutically acceptable salts and individual diastereomers thereof.

Most preferred compounds of the instant invention are realized in structural formula V:

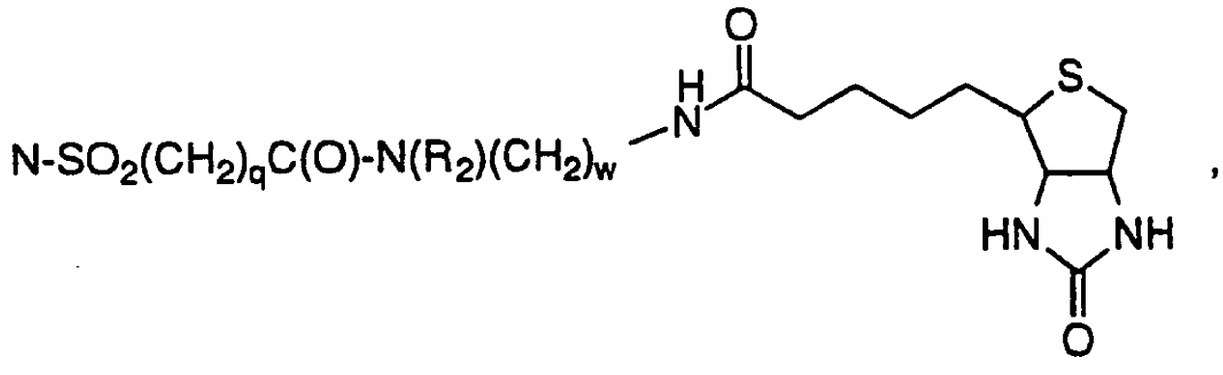


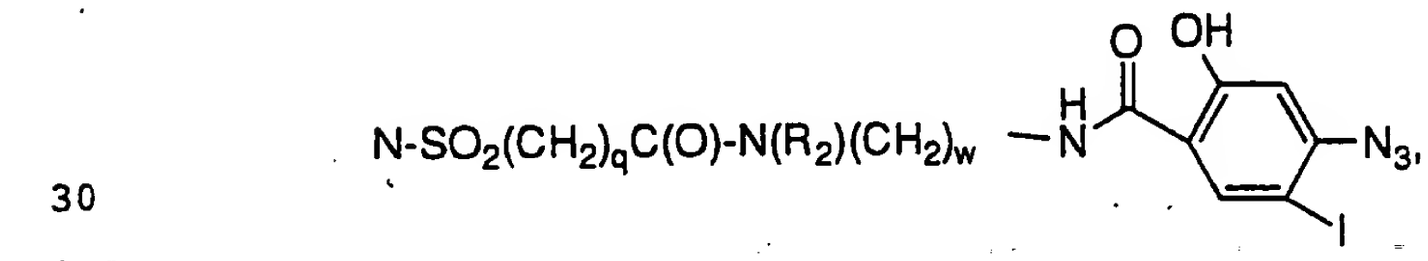
V

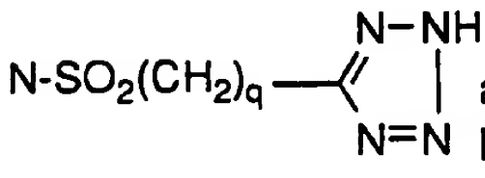
R_1 is  ;  ,  ,  ,  ,  ,  ,  ;  ;  ;

R_{3a} is H, fluoro;

D is O, S, $S(O)_m$, $N(R_2)$, $NSO_2(R_2)$, $NSO_2(CH_2)_t$aryl, $NC(O)(R_2)$, $NSO_2(CH_2)_qOH$, $NSO_2(CH_2)_qCOOR_2$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(R_2)$, $N\text{-}SO_2(CH_2)_qC(O)\text{-}N(R_2)(CH_2)_wOH$,

 ,

 ,

 and the aryl is phenyl or pyridyl and the phenyl may be substituted by 1-2 halogen;